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(54) Title: SUBSTITUTED N-BENZENESULFONYLOXYPHTHALIMIDES

(57) Abstract

Substituted N-benzenesulfonyloxyphthalimides having substantial cytotoxic activity of long duration and at low concentration are provided as antineoplastic chemotherapeutic agents having a low potential for toxic effect on normal tissue. The compounds have favorable activity as antiviral agents and as inhibitors of ribonucleotide reductase.

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SUBSTITUTED N-BENZENESULFONYLOXYPHTHALIMIDES

Field of the Invention

The present invention relates generally to anticancer and antiviral drugs, and more particularly to substituted N-benzenesulfonyloxyphthalimides and a process for their production.

Background and Summary of the Invention

Antineoplastic agents comprise a large group of chemical compounds. Such drugs are the main avenue of treatment for generalized forms of cancer, such as leukemias and malignancies of the lymphatic system, which cannot be attacked by surgery or irradiation. Such chemical agents include polyfunctional alkylating compounds such as nitrogen mustard, triethylene melamine and triethylene thiophosphoramide which produce temporary remission in chronic leukemia. Other compounds, sometimes referred to as antimetabolites, interfere with tumor metabolism in various ways, such as by substituting a metabolic analog for an essential amino acid, or by the competitive inhibition of an enzyme necessary for DNA synthesis and cellular replication. Two particular classes of enzyme inhibitors are folic acid reductase inhibitors (e.g. methotrexate) and ribonucleoside diphosphate (ribonucleotide) reductase inhibitors.

The biosynthesis of deoxyribonucleotide from ribonucleotides is one of the crucial and rate limiting steps in DNA synthesis in mammalian cells, as the pool size of deoxyribonucleotides in such cells is not adequate to support DNA synthesis for more than a brief period. High concentrations of deoxyribonucleotides are also required for maximal DNA synthesis rates. Ribonucleotide reductase, the enzyme that catalyzes the reduction of ribonucleotides to deoxyribonucleotide, is therefore intimately associated with the replication of the cell, and there is an excellent correlation between ribonucleotide reductase activity and tumor growth rate.

Antineoplastic agents often have undesirable side effects and must be discontinued after a certain dosage level is reached. Methotrexate for example, while a beneficial cancer drug, has a high potential toxicity, usually dose-related. When the maximum dose of one class of drugs is reached, as in the case of treatment with a folate inhibitor, therapy may be continued with ribonucleotide reductase inhibitors such as hydroxyurea or thiosemicarbazones which may have similar cytotoxic effects on neoplastic tissue without identical side effects.

With regard to ribonucleotide reductase inhibitors, hydroxyurea is presently the drug of choice for clinical use. Hydroxyurea has been used beneficially and extensively in the treatment of cancers, and may be administered either orally or intravenously. Due to the fact that hydroxyurea is a small molecule and highly water soluble, the drug is eliminated rapidly and

approximately 80% of an oral or intravenous dose of 7 to 30 mg/kg may be recovered in the urine within 12 hours. As a result of this rapid elimination, large doses are required to maintain the desired cytotoxic effect. Such large doses, in turn, have the potential of causing gastrointestinal irritation, bone marrow depression, and other damaging side effects on normal tissue. Nonetheless, hydroxyurea remains the accepted drug in cases of melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic or inoperable carcinoma of the ovary. In addition, it may be used concomitantly with irradiation therapy in the control of primary squamous cell carcinomas of the head and neck.

As to other ribonucleotide reductase inhibitors, guanazole has been used clinically, but only to a limited extent, in the treatment of certain adult leukemias. Extensive clinical use of both guanazole and hydroxyurea is limited by their high polarities, low molecular weights, fast elimination rates and subsequent low therapeutic indices. Thus frequent dosing and continuous intravenous infusions are usually needed to attain efficacy.

Another group of ribonucleotide reductase inhibitors which has been used experimentally as a cancer chemotherapeutic agent is the a-(N)-heterocyclic carboxaldehyde thiosemicarbazones. The pharmacological disposition of 5-hydroxy-2-formyl pyridine thiosemicarbazone(NSC 107392) was studied in Phase I and has thus far proven to be ineffective in man. Administration of larger doses of the drug was limited

by gastrointestinal toxicity, myelosuppression, hemolysis and anemia. MAIQ-1(4-methyl-5-Amino-1-Formyl Isoquinoline thiosemicarbazone) is a second generation antineoplastic agent of the α-(N)-heterocyclic carboxaldehyde thiosemicarbazone class. It has significant activity against a number of transplantable tumors and inhibits RDR from Novikoff rat tumor. It is currently in Phase I trial.

Another drug currently in Phase I trials is 2,3-dihydro-1H-imidazo(1,2-b) pyrazole which has been shown to be effective in L1210 leukemia cells resistant to guanazole and the thiosemicarbazones. However, no definite tumor regression was seen in pateients with refractory metastatic solid tumors, while dose limiting hemolysis, nausea, vomiting and fatigue was encountered at high doses.

Various indices have been developed to quantify the therapeutic efficiency of anticancer and antiviral formulations. For example, the term "ID_{50}" represents the concentration, expressed as molarity, required for a 50% inhibition of cell growth in standardized cells such as Murine leukemia L-1210 cells. The term "LD_{50}" represents the dose needed to kill 50% of the animals in an in vivo test. Thus, the terms ID_{50} and LD_{50} represent, respectively, the desirable and undesirable effects of the formulation and are often combined to show therapeutic efficiency and expressed as a "therapeutic index" i.e. the ratio of the LD_{50} to the ID_{50}. Thus, an increase in the numerical value of the therapeutic index has a direct relationship to an increase in therapeutic efficiency.

For example, the LD_{50} of hydroxyurea is 7,330 mg/kg in mice. Physicians' Desk Reference, 33rd Ed. 1979, pp. 1645-6. The ID_{50} for hydroxyurea, for L-1210 tumor cells, is 1×10^{-3} molar. The division of the LD_{50} by the ID_{50} concentration (expressed in mg/kg) yields a therapeutic index of 96.

According to the present invention, novel substituted N-benzenesulfonyloxyphthalimides are provided having superior therapeutic efficiency as anticancer and antiviral agents. The compounds comprise derivatives of N-benzensulfonyloxyphthalimide wherein the derivatives are substituted, at the fourth position of the phthalimide ring, with a hydrophilic substituent such as amino, hydroxyl or other substituents. The compounds comprise a substantially lipophilic molecule of relatively high molecular weight with a hydrophilic substituent providing sufficient polarity to provide the described physiological effect.

A novel synthetic method for the preparation of such compounds is also provided. Substituted phthalic acid or phthalic acid esters are treated with hydroxylamine to form a salt of the corresponding N-hydroxyphthalimide, which is then reacted with benzenesulfonyl chloride or bromide to form the substituted N-benzenesulfonyloxyphthalimide.

The compounds of the present invention provide a new class of ribonucleoside diphosphate

reductase inhibitors of increased molecular size and decreased water solubility which retain substantial hydrophilic properties. The compounds inhibit a growth of cancer cells at effective doses of less than 1% of the prior art formulations, and provide a therapeutic index more than 100 times greater than that of the ribonucleotide reductase inhibitors which are presently known.

DETAILED DESCRIPTION

While the invention will be exemplified by reference to a specific substituted N-benzenesulfonyloxy-phthalimide, the invention in general and certain aspects in particular are broad in scope, for example, the concept of the substitution of N-benzenesulfonyloxy-phthalimides with a hydrophilic substituent to produce formulations having the effects hereinafter set forth.

Further, the process of the present invention contemplates the formation and use of any phthalic acid ester which is appropriate for the production of the described compounds. Lower aliphatic ester groups such as methyl, propyl and butyl, as well as the ethyl ester hereinafter described, are particularly useful.

The hydrophilic substituent may be selected from groups which suitably bond to the fourth position of the phenyl ring, as described, and which are sufficiently hydrophilic to produce a π value of less than zero as set forth in C. Hansch, et al., Substituent Constants for Correlation Analysis in Chemistry and

Biology, Wiley-Interscience, New York, 1979. In this regard, the following substituents have been found to be useful:

R	π Value
NH_2	-1.23
OH	-0.67
$NHCONH_2$	-1.30
$NHCSNH_2$	-1.40
$NHCOCH_3$	-0.97
NHOH	-1.34
$NHNH_2$	-0.88
NHCHO	-0.98
$NHSO_2CH_3$	-1.18

The specific details hereinafter described afford the best embodiments known at this time to provide a basis for the claims which define the scope of the present invention.

EXAMPLE I

A mixture of 3 and 4-nitro phthalic acids (38g;0.2m) was refluxed with 100 ml of absolute ethanol for 24 hours after saturating the solution with HCl gas. After removal of the solvent, the yellow solid was dissolved in chloroform, washed with water (3 x 100ml) and washed with 10% Na_2CO_3 (2 x 100 ml). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to yield a brown oil which was subsequently distilled to afford 31 g(81%) of 4-nitrodiethyl phthalate; b.p 188-190°C.

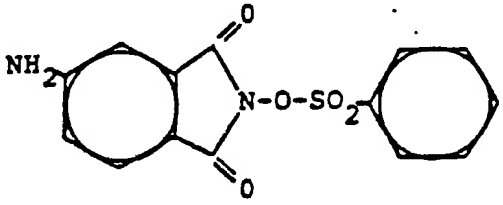
A suspension of 4-nitrodiethyl phthalate (56g; 0.21M) and platinum oxide (0.1g) in 100 ml of absolute ethanol was reduced under hydrogen pressure for 90 minutes. The ethanol was removed after filtering off the catalyst and the resulting yellow solid was recrystallized from ethanol-benzene to yield 40-g(80%) of 4-aminodiethyl phthalate m.p 92-93°C.

To an ethanolic solution of 4-aminodiethyl phthalate (11.5g;0.048M/3g sodium in 100 ml ethanol) was added an ethanolic solution of hydroxylamine (4.3g;0.05M) such that the temperature was maintained at 20°C. The flask was stoppered and left standing at 0°C for 2-4 hours. Petroleum ether was then added to the gelatinous mass and the suspension was filtered. The orange solid was dried under a vacuum for 8 hours and immediately used for the next step (9.8g-80%).

The crude sodium salt of 4-amino-N-hydroxy-phthalimide (2g;0.01M) was added to 30 ml chloroform and stirred for 30 minutes. Then benzenesulfonyl chloride (2g;0;01M) was added over a period of 30 minutes at 25°C and the solution was left standing for 1-2 hours. The resulting suspension was filtered and 30 ml ethanol was added to the filtrate. A yellow solid precipitated and was collected. It was then recrystallized from ethanol-benzene to yield 2.5g(78%) of 4-amino-N-benzenesulfonyloxyphathalimide, m.p. 195-196°C. Analyzed $C_{14}H_{10}N_2O_5S$ (C,H,N):

	Calculated	Observed
C	52.81	53.03
H	3.16	3.42
N	8.80	8.74

Nuclear magnetic resonance and infrared spectrophotometer testing, as well as elemental micro analysis, showed the following structure for the compound 4-amino-N-sulfonyloxyphthalimide produced in Example I:



The compounds of the present invention may also be produced without the esterification reaction by the similar treatment of substituted phthalic acid with hydroxylamine. For example, 4-nitrophthalic acid may be reduced under hydrogen pressure in the presence of platinum oxide in ethanol to yield 4-aminophthalic acid, which is then caused to react with an ethanolic solution of hydroxylamine, produced from a mixture of hydroxylamine hydrochloride and sodium ethoxide to form a sodium salt of the 4-amino-N-hydroxyphthalimide. Subsequent treatment with benzenesulfonyl chloride will yield the 4-amino-N-benzenesulfonyloxyphthalimide herein described.

Other hydrophilic molecules may be substituted for the fourth position amino by methods known in the art. 4-amino phthalic acid or a 4-amino phthalic acid ester may be diazotized with nitrous acid to enable such substitution. For example, the reaction with nitrous acid and steam in the presence of heat will produce 4-hydroxyphthalic acid or the corresponding ester.

EXAMPLE II

The therapeutic efficiency of 4-amino-N-sulfonyloxyphthalimide and other compounds was tested, first with regard to inhibitory action on L-1210 tumor cells in vitro.

L1210 cells were maintained in asynchronous logarithmic growth at 37°C in a media supplemented with 10% fetal calf serum, 1% penicillin, and 1% streptomycin. The cells were grown in a humidified incubator supplied with 95% air and 5% carbon dioxide at 37°C. Stock cells were suspended at 6000-9000 cells/ml. The pH of the experimental flasks was adjusted to 7.4 with the addition of carbon dioxide.

The drugs were solubilized with 1% dimethyl sulfoxide, diluted in phosphate-buffered saline, and added to the cell culture in 1:10 dilution in an amount sufficient to achieve the desired drug concentration. The cell cultures were provided at 5000 cell/ml in duplicate for each drug concentration in 25 cm^2 flasks.

After 24, 48 and 72 hours of continuous drug exposure, the cells were harvested and counted by means of a Coulter counter. As a control, a 1% dimethyl sulfoxide-treated set of cultures was included for each separate dose-response test.

The drug concentration required for the 50% inhibition of cell growth (ID_{50}) was determined for each compound, and the results are reported in Table I.

EXAMPLE III

The antiviral activity of 4-amino-N-sulfonyloxy-phthalimide in vitro against the transformation of Rous Sarcoma virus (Avian oncovirus) in chicken fibroblast was determined, following the procedure detailed in Methods in Virology, Vol. 3, K.Maramorosch et al. At a concentration of 2.74×10^{-5} M, the compound exhibited a 63% and 38% inhibition for 10,000 and 20,000 viral particles per plate, respectively. At a concentration of 1.37×10^{-5} M, the compound showed an inhibition of 75% and 26%, for 10,000 and 20,000 viral particles per plate, respectively. At 6.85×10^{-5} M, the compound showed some cytotoxicity to the chicken fibroblast in the tissue culture. The ID_{50} of hydroxyguanidine sulfate, a known antiviral agent, is 7.21×10^{-5} M under the same conditions at a population of 20,000 viral particles per plate.

EXAMPLE IV

The acute lethal toxicity of 4-amino-N-sulfonyloxyphthalimide was determined by the following method.

As the compound retains such lipophilic properties so as to have insufficient solubility in water for purposes of intraperitoneal injection, the compound was suspended as a fine powder in 5% aqueous acacia solution. This suspension was then injected intraperitoneally in C57-BL/6j mice weighing 16-26 grams. Six animals (three males and three females) were used for each dosage studied, and the animals were observed for 72 hours for any apparent signs of toxicity. The dosages used were 75 mg/kg (3.75 mg/cc), 100 mg/kg (5 mg/cc), 250 mg/kg (12.5 mg/cc), 500 mg/kg (25 mg/cc) and 1,000 mg/kg (50 mg/cc).

No apparent sign of toxicity was observed in any of the animals tested. Some animals were sacrificed after 72 hours and the body cavity was examined. Residues of unabsorbed yellow powder were observed, reflecting the incomplete absorption of the compound injected. Thus, the LD_{50} in mice is at least as high as 1,000 mg/kg.

Using the ID_{50} and LD_{50} values for 4-amino-N-benzenesulfonyloxyphthalimide, and hyroxyurea, the therapeutic index for each was calculated and reported

in Table I. As an example, the therapeutic index for 4-amino-N-benzenesulfonyloxyphthalimide was calculated by dividing the LD_{50} of greater than 1,000 by the ID_{50} value expressed in milligrams i.e. 2.28×10^{-6} x molecular weight (318) x 10^3 = a therapeutic index of >1,379. Similarly, the LD_{50} of hydroxyurea (7330 mg/kg) was divided by the ID_{50} of 1×10^{-3} x molecular weight (76) x 10^3 to yield a therapeutic index of 96.

EXAMPLE V

The inhibition of rat ribonucleotide reductase by hydroxyurea and 4-amino-N-benzenesulfonyloxyphthalimide were tested by incubating various concentrations of the drugs with an incubation mixture containing 0.8% DMSO, 2.1 mM ATP, 6.3 mM MgAc, 20μM $Fe(NH_4)_2(SO_4)_2$, 6.3 mM dithiothreitol, 8.3 mM phosphate buffer pH 7, 170 μM $^{32}_{p}$-CDP and partially purified rat ribonucleotide reductase and thioredoxin sufficient to reduce 4 nmoles CDP in 30 minutes in the control. The results are shown in Table II.

As is apparent from the examples, the novel compounds described therein inhibit growth of tumor cells at an effective dose of less than 1% of that of the currently used chemotherapeutic agent. The higher molecular weight and lipophilicity of the compounds yield longer duration of drug action and substantially improved LD_{50} values. Even absent the increased cytotoxic activity of the compounds of the present invention, the high molecular weight and substantial

lipophilicity of the compounds present a beneficial alternative treatment in patients where drug resistance has been developed to other classes of chemotherapeutic agents or to the highly polar ribonucleotide reductase inhibitor hydroxyurea. The favorable antiviral activity of the compounds, as compared to existing drugs, makes it a suitable agent for the prevention of viral transformation of normal cells. We contemplate the administration of the drug in tablet or capsule form, although the compounds may be presented to the patient according to other methods. In addition to drug use, the novel compounds are useful as biochemical tools as inhibitors of ribonucleotide reductase.

Although the foregoing invention has been described in some detail by way of illustration and example, changes in form and the substitution of equivalents are contemplated as circumstances may suggest or render expedient; and although specific terms have been employed herein, they are intended in a descriptive sense and not for purposes of limitation, the scope of the invention being delineated in the following claims.

TABLE I

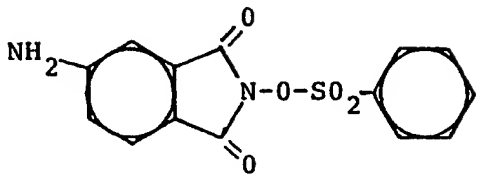
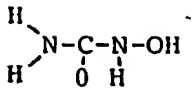
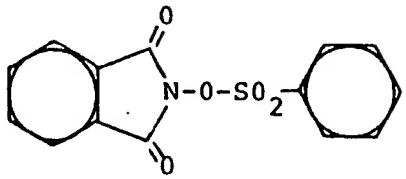
Compound	ID_{50}	LD_{50} mg/kg	Therapeutic Index
4-amino-N-benzenesulfonyloxyphathalimide 	2.28×10^{-6}M	>1,000	>1,370
Hydroxyurea 	1×10^{-3}M	7,330	96
N-benzenesulfonyl-oxyphthalimide 	4.42×10^{-6}M	-	-

TABLE I (Continued)

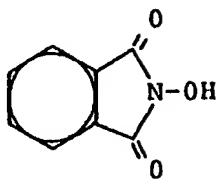
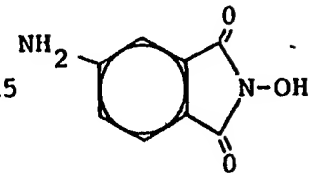
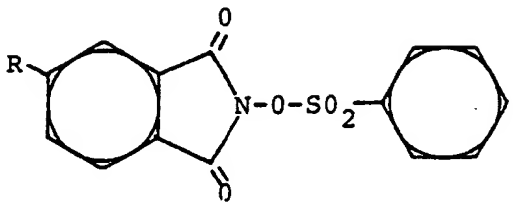
Compound	ID_{50}	LD_{50} mg/kg	Therapeutic Index
N-hydroxyphthalimide 	1.17×10^{-5}M	-	-
4-amino-N-hydroxyphthalimide 	1.79×10^{-4}M	-	-

TABLE II

Drug	Concentration (mM)	% Inhibition
hydroxyurea	0.1	42
	0.4	71
	1.0	87
4-amino-N-sulfonyloxy-phthalimide	$\leq$0.1	3
	$\leq$1.0	19
	$\leq$10.0	67

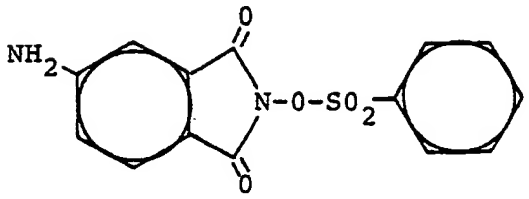
WHAT IS CLAIMED IS:

1. A substituted N-benzensulfonyloxy-phthalimide of the formula

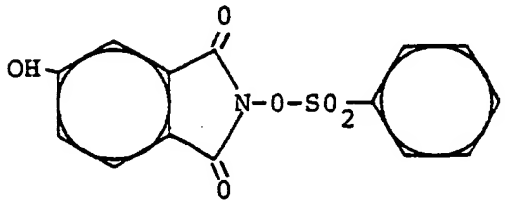


in which R is selected from the group consisting of NH_2, OH, $NHCONH_2$, $NHCSNH_2$, $NHCOCH_3$, NHOH, $NHNH_2$, NHCHO and $NHSO_2CH_3$.

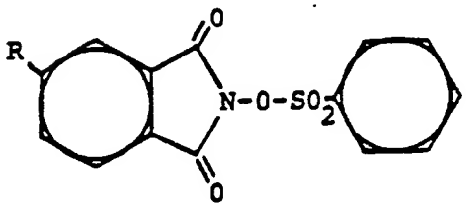
2. 4-amino-N-benzenesulfonyloxyphthalimide of the formula



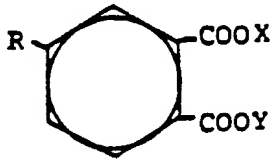
3. 4-hydroxy-N-benzenesulfonyloxyphthalimide of the formula



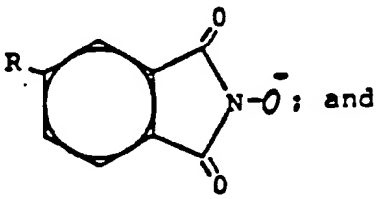
4. A process for the production of a substituted N-benzen sulfonyloxyphthalimide having the formula



which comprises reacting substituted phthalic acid or a phthalic acid ester having the formula



wherein R is selected from the group consisting of NH_2, OH, $NHCONH_2$, $NHCSNH_2$, $NHCOCH_3$, NHOH, $NHNH_2$, NHCHO and $NHSO_2CH_3$ and X and Y, the same or different, are selected from the group consisting of hydrogen, methyl, ethyl, propyl and butyl; with hydroxyl amine to form a moiety having the formula



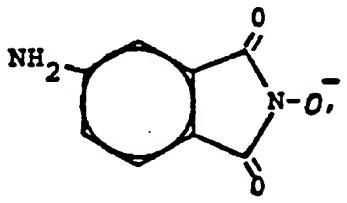
; and

substantially reacting said moiety with benzenesulfonyl chloride or bromide.

5. The process according to Claim 4 wherein R is NH_2, and X and Y are ethyl.

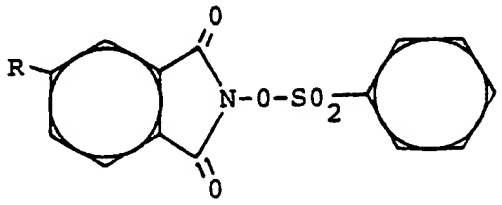
6. A process for the production of 4-amino-N-benzenesulfonyloxyphthalimide which comprises reacting 4-aminodiethylphthalate with hydroxylamine to form 4-amino-N-hydroxy-phthalimide, and reacting said 4-amino-N-hydroxy-phathalimide with benzenesulfonyl chloride or bromide.

7. A process for the production of 4-amino-N-benzenesulfonyloxyphthalimide which comprises reacting 4-aminophthalic acid with hydroxylamine to form a moiety having the formula



and subsequently reacting said moiety with benzensulfonyl chloride or bromide.

8. A method for the treatment of neoplastic and viral disorders in a mammal which comprises administering to said mammal a substituted N-benzenesulfonyloxyphthalimide of the formula



in which R is selected from the group consisting of NH_2, OH, $NHCONH_2$, $NHCSNH_2$, $NHCOCH_3$, NHOH, $NHNH_2$, NHCHO and $NHSO_2CH_3$.

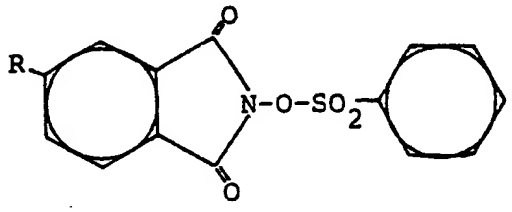
9. The method of Claim 8 wherein R is NH_2.

10. The method of Claim 8 wherein R is OH.

AMENDED CLAIMS

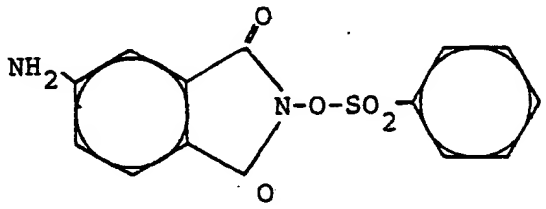
[received by the International Bureau on 03 January 1984 (03.01.84);
original claims 1 t 10 replaced by claims 1 to 18]

1. A biologically-active composition comprising 4-hydroxy-N-benzenesulfonyloxyphthalimide of the formula



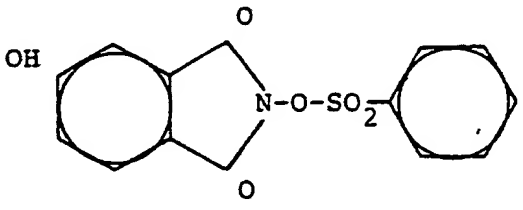
together with an appropriate carrier therefor.

2. A biologically-active composition comprising a substituted N-benzenesulfonyloxyphthalimide of the formula



in which R is selected from the group consisting of NH_2, OH, $NHCONH_2$, $NHCSNH_2$, $NHCOCH_3$, NHOH, $NHNH_2$, NHCHO and $NHSO_2CH_3$, together with an appropriate carrier therefor.

3. A biologically-active composition comprising 4-amino-N-benzenesulfonyloxyphthalimide of the formula



together with an appropriate carrier therefor.

4. The composition of claim 1 wherein the composition is chemotherapeutic and the carrier is pharmaceutically acceptable.

5. The composition of claim 2 wherein the composition is chemotherapeutic and the carrier is pharmaceutically acceptable.

6. The composition of claim 3 wherein the composition is chemotherapeutic and the carrier is pharmaceutically acceptable.

7. The composition of claim 1 wherein the composition is cytotoxic and the carrier is pharmaceutically acceptable.

8. The composition of claim 2 wherein the composition is cytotoxic and the carrier is pharmaceutically acceptable.

9. The composition of claim 3 wherein the composition is cytotoxic and the carrier is pharmaceutically acceptable.

10. The composition of claim 1 wherein the composition is antiviral and the carrier is pharmaceutically acceptable.

11. The composition of claim 2 wherein the composition is antiviral and the carrier is pharmaceutically acceptable.

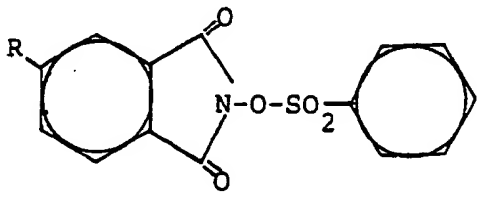
12. The composition of claim 3 wherein the composition is antiviral and the carrier is pharmaceutically acceptable.

13. The composition of claim 1 wherein the composition inhibits the formation of ribonucleotide reductase.

14. The composition of claim 2 wherein the composition inhibits the formation of ribonucleotide reductase.

15. The composition of claim 3 wherein the composition inhibits the formation of ribonucleotide reductase.

16. A method for the treatment of neoplastic and viral disorders in a mammal which comprises administering to said mammal a substituted N-benzenesulfonyloxy-phthalimide of the formula



in which R is selected from the group consisting of NH_2, OH, $NHCONH_2$, $NHCSNH_2$, $NHCOCH_3$, NHOH, $NHNH_2$, NHCHO and $NHSO_2CH_3$.

17. The method of claim 16 wherein R is NH_2.

18. The method of claim 16 wherein R is OH.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US83/01328

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl3 A61K 31/40; C07D 209/48;
U.S. Cl. 424/274; 548/475

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U. S.	424/274; 548/475;

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

Chemical Abstracts-Vol. 56-75: Phthalimide;Vol. 76-97; 1H-Isoindole-1,3-dione; Vol. 56-97: Formula Index $C_{14}H_9NO_5S$, $C_{14}H_9NO_6S$, $C_{14}H_{10}N_2O_5S$;

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X,Y	US, A, 4,258,121, KOJIMA, published 1981, March 24; see column 2, lines 5-19; column 3, lines 25-66,	1-3, 4-7
A	US, A, 2,816,111, WEGLER ET AL., published 1957, December 10; see column 1, lines 25-54.	1-3
Y	US, A, 2,863,801, KUHLE ET AL., published 1958, December 9; see column 1, lines 32-40.	4-7

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]
27 October 1983

Date of Mailing of this International Search Report [2]
09 NOV 1983

International Searching Authority [1]
ISA/US

Signature of Authorized Officer [20]
M. C. Eakin